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ARTICLE

In/out isomerism of cyclophanes: a theoretical account on 2,6,15-trithia-[3^{4,10}][7]metacyclophane and [3^{4,10}][7]metacyclophane, as well as their halogen substituted analogues

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A detailed theoretical investigation of cyclophanes with a divergent set of methods, ranging from molecular mechanics through semiempirical to ab intio is presented. Cyclophanes have attracted interest over the years due to their unusual chemistry and increasing applications. There has been previous debate over the effects contributing to the greater stability of more crowded in isomers of certain cyclophanes and higher strain in the out isomer was the prevailing explanation. Application of EDA-NOCV and SAPT analysis has enabled us to distinguish between different effects controlling isomer stability and determine the significance of all effects involved. Our results show that, although strain has a large significance, orbital stabilization within the molecule from the aromatic electron density is crucial. Furthermore, we analysed halogen substituted cyclophanes in order to further understand these subtle effects.

1 Introduction

One of the most important challenges of computational chemistry is the accurate prediction of geometry and stability of isomers and the complete understanding of all structure determining factors. This task is difficult in the case of crowded and strained molecules such as cyclophanes.[1, 2] Cyclophanes are molecules which have more than two atoms of an aromatic ring incorporated into a larger ring system, that is, at least two non-adjacent atoms on the ring are connected with an aliphatic chain.[3-5] There has been great interest in cyclophane chemistry[6] due to their unique properties[7-10] arising from proximity of either aromatic rings, or atoms and groups to an aromatic ring. They have found applications in polymers and material science,[11] metal-ion receptor structures[12, 13] and are promising catalysts.[14]

Known members of the cyclophane family are *in*-2,6,15-trithia-[3^{4,10}][7]metacyclophane[15] and its comparably congested hydrocarbon analogue *in*-[3^{4,10}][7]metacyclophane[16] (Fig. 1), which have a methine hydrogen projected to the centre of the aromatic ring. There has been a debate whether larger trithiacyclophanes,[15, 17, 18] with similar structures to the previously mentioned trithiacyclophane, are *out* or *in* isomers, which was concluded in favour of the latter. Previous research suggested that formation of the *in* isomer in the macrocyclic reaction is only due to a high degree of angle strain in the *out* isomer.[19] This was corroborated by MM2 calculations that indicated relative stability of the *in*-trithiacyclophane by 7 kcal/mol[15] and justified the claim that strain is mainly responsible for *in* isomer formation. However, proximity of the hydrogen atom to the aromatic ring has raised questions regarding the role of the CH/π interaction in stabilization of the *in* isomers.[20] Previous experimental and theoretical investigations[21-23] on methane-benzene model systems have shown that benzene-methane complex prefers a geometry in which the methane C-H bond points toward the centre of the benzene ring, similar to the geometry found in *in*-2,6,15-trithia-[3^{4,10}][7]metacyclophane and its hydrocarbon analogue. Methane/benzene interaction energy was determined with mass analysed threshold ionization technique to be in the range of 1.03-1.13 kcal/mol.[21] Results of the high level *ab initio* theoretical calculations are in good agreement with experimentally found binding energy: CCSD(T) calculations at complete basis set limit and corrected for vibrational zero-point energies estimated the binding energy at 1.132 kcal/mol[21], while symmetry-adapted perturbation theory (SAPT) calculations predicted the binding energy to be 1.014 kcal/mol.[23]

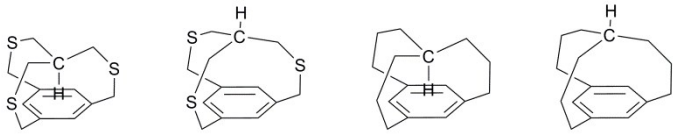

Fig. 1 Structures of in/out-2,6,15-trithia-[3^{4,10}][7]metacyclophane and in/out-[3^{4,10}][7]metacyclophane, respectively

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A few theoretical studies have argued inadequacies of some Density Functional Theory (DFT) methods in accurate description of geometry of various cyclophanes,[1, 2] in particular B3LYP[24, 25]. On the contrary, a study by Truhlar and Zhao[26] shows the aptness of DFT in handling geometry descriptions of these molecules.

The aim of this work was to determine the factors which govern preferential formation of cyclophane isomers and investigate performance of different levels of theory, from molecular mechanics to *ab initio*. Furthermore, studies of functional group interaction resulting from enforced mutual proximity are a major theme of cyclophane chemistry.[27] Bearing this in mind, we explored how substitution of the hydrogen atom protruding towards the aromatic ring with a halogen (fluorine, chlorine and bromine) reflects on isomer relative stability. An elegant way of isolating individual contributions in bond formation is by Extended Transition State Energy Decomposition Analysis (EDA)[28-30] alongside Natural Orbitals for Chemical Valence (NOCV)[31, 32] sheme. Also, in order to examine the nature and contribution of CH/π and CX/π interactions in cyclophane isomers stability extensive SAPT calculations were performed on model systems. With this study we hope to have had shed a light on the forces governing cyclophane isomer stability.

2 Methods

Structural optimizations of the investigated molecular systems were carried out in Orca (version 3.03)[33] and Amsterdam Density Functional[34, 35] (ADF) molecular modelling suite (version 2013). Taken aback by some of the previous reports that the HF/3-21G* method gave very accurate estimations of nonbonded contacts in various cyclophanes[2] an extensive systematic investigation using different levels of theory was conducted. The geometry optimization was carried out with Orca using Pople's 6-31G(d) basis set together with MP2[36, 37] method and M06-2X,[38] LDA,[39] B3LYP[24, 25] and BP86[40-42] functionals within the DFT framework. However, the HF[43] method was utilized using the 3-21G basis set, in accordance with previous claims of its suitability.[2] Additionally, optimization was repeated using Grimme's third generation dispersion energy correction[44-47] and Becke-Johnson damping,[47] i.e. D3 with all the methods, except LDA/6-31G(d) and M06-2X/6-31G(d). To investigate how subtle changes in basis set constitution may affect optimization, an all electron triple-ξ Slater-type orbitals plus one polarization function (TZP) basis set was put to use alongside PBE[48] with dispersion correction (PBE-D3), LDA and M06-L[49, 50] functionals in ADF. Also, additional calculations in ADF were performed on in-2,6,15-trithia-[3^{4,10}][7]-metacyclophane using M06-2X with TZP and PBE-D3 with a valence quadruple-ξ Slater-type orbitals plus four polarization functions (QZ4P) basis, and in Orca B3LYP with aug-cc-pVTZ basis, in order to check the influence of a larger basis set.

Harmonic frequencies were calculated at the corresponding level of theory in order to confirm correspondence of the optimized structures to the minima on the potential energy surface.[51, 52]

To further explore the nature of cyclophanes, EDA analysis as implemented in ADF was used. The underlying principle of EDA is separation of individual contributions to the binding energy E_{bind} of two fragments that form a molecule. This energy can be expressed as a sum of preparation, E_{prep}, and interaction energy, E_{int}, with the former defined as the energy needed to transform the fragments from their equilibrium structures to the geometry they embrace in the molecule. The latter, E_{int}, can be further decomposed into several contributions: E_{el} is the classical electrostatic interaction; E_{Pauli} accounts for the repulsion between the occupied orbitals of the two fragments; E_{orb} is a stabilizing contribution originating from interaction between occupied and unoccupied orbitals on opposite fragments as well as polarization on individual fragments, and E_{disp} is the dispersion correction contribution if Grimme's dispersion energy correction (D3) is included. Coupled with NOCV decomposition of electron density deformation,[31, 32] EDA analysis was performed to establish the most important density transfer channels either by the amount of charge transfer, or as energy contribution to the E_{orb}. The choice of fragments for EDA-NOCV analysis fell to the methine hydrogen or halogen and the rest of the molecule, that is, the remaining cage. EDA-NOCV analysis has been performed on the LDA/TZP geometries. Nevertheless, it is known that LDA shows overbinding effects[53] and therefore not suitable for a detail energetic analysis. Instead, the PBE-D3 functional was employed along with TZP basis. EDA-NOCV analysis was additionally conducted on the X-ray geometry of in-2,6,15-trithia-[3^{4,10}][7]metacyclophane[15] obtained from the Cambridge Crystallographic Database[54] (ref. code VAMMEB), as well as on M06-2X/TZP, M06-L/TZP and PBE-D3/QZ4P geometries of in/out-2,6,15-trithia-[3^{4,10}][7]metacyclophane with M06-2X/TZP, M06-L/TZP and PBE-D3/QZ4P methods.

In order to investigate the importance of CH/π and CX/π interactions on stability of *in*-isomers of cyclophanes, symmetry-adapted perturbation theory method with density-fitting approximation (DF-SAPT2+3)[55, 56] calculations were employed on model systems. This perturbational method enables direct computation of interaction energy between monomers and can provide a decomposition of total interaction energy into four physically meaningful terms: electrostatic, exchange-repulsion, induction and dispersion. In short, electrostatic energy term represents the energy of the electrostatic (Coulombic) interaction of the unperturbated monomers charge distributions; exchange-repulsion energy term mainly corresponds to the effect of Pauli repulsion, i.e. antisymmetrization of the wavefunction for exchange of electrons between monomers; induction term is the energy of

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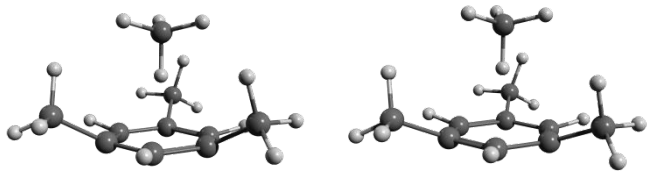

Fig. 2 3D structures of model system 1 and 2 given respectively

interaction between induced multipole moments of one monomer in the static electric field of the other monomer and dispersion energy term can be attributed to the interactions of instantaneous electric multipole moments of the monomers.[57] The model systems for DF-SAPT2+3 calculations (Fig. 2) were created from LDA/TZP optimized geometries of *in*-[$3^{4,10}$][7]metacyclophane (model system 1) and *in*-2,6,15-trithia-[$3^{4,10}$][7]metacyclophane (model system 2) by removing the bridging methylene groups and/or sulphur atoms and substituting them with hydrogen atoms. The geometry and mutual orientation of the two created closed-shell fragments remained the same as in the investigated cyclophanes. Standard aug-cc-PVTZ basis set was employed for all DF-SAPT2+3 calculations with aug-cc-PVTZ-JKFIT as auxiliary basis set for SCF density fitting computations and aug-cc-PVTZ-RI as auxiliary basis set for SAPT density fitting computations. DF-SAPT2+3 calculations were performed using PSI4 program.[58]

3 Results and discussion

3.1 Geometry optimization

We have examined optimized structures of two comparably congested cyclophanes, *in/out*-2,6,15-trithia-[$3^{4,10}$][7]meta-cyclophane and *in/out*-[$3^{4,10}$][7] metacyclophane, along with their halogen substituted analogues (Fig. 3). Of all the studied cyclophanes, the only available experimental X-ray crystallographic structure is of *in*-2,6,15-trithia-[$3^{4,10}$][7] metacyclophane[15] from the Cambridge Crystallographic Database[54] (ref. code VAMMEB). The in-2,6,15-trithia-[$3^{4,10}$][7]-metacyclophane structure was optimised with several DFT functionals and the obtained geometrical parameters were compared to the X-ray structure[15], as shown in Table 1, where mean signed (MSE) and mean unsigned errors (MUE) are also given. We note that M06-2X and M06-L functionals gave results in good agreement with the experimental structure, which is in accordance with previous DFT calculations done on cyclophanes.[26] Also, optimization with the simplest of employed functionals (LDA) gave good accordance with the X ray structure, as seen by MSE/MUE values, Table 1. It is not surprising that the LDA showed such agreement with the experiment, since overbinding effects[53] of LDA may echo the strong packing forces present in crystal environments. This is especially relevant for high symmetry molecules (*in* isomer belongs to C_3 symmetry point group) upon which the forces act equally on several parts of the molecule,[2] which is different than a theoretical consideration of a single molecule in vacuum. Enlarging the basis set makes slight improvements in optimized geometries, as seen with the use of PBE-D3 with Slater type TZP and QZ4P basis, and B3LYP-D3 with Gaussian type 6-31G(d) and aug-cc-pVTZ, Table 1. Hybrid functionals and older GGA's, i.e. B3LYP and BP86, show poor handling of geometrical parameters, as reported previously.[1, 2, 26] However, using Grimme's third generation dispersion energy correction[44-47] and Becke-Johnson damping,[47] a molecular mechanics-like correction, improves agreement with the experimental structure and the MSE/MUE values are significantly lower for B3LYP and BP86 with the correction than without. Minnesota functionals[26, 49, 50] perform well since they already contain medium-range overlap-dispersive and steric exchange repulsion effects implicitly, as opposed to the additional dispersion correction (e.g. D3[46]).

Table 2 and 3 list calculated relative energies and intramolecular nonbonded contacts for *in/out*-(halogen)-2,6,15-trithia-[$3^{4,10}$][7]metacyclophane and *in/out*-(halogen)-[$3^{4,10}$][7]metacyclophane, respectively. In order to check the performance of different methods results obtained with molecular mechanics (MM), and semi-empirical Density Functional based Tight Binding[59] (DFTB), as well as DFT with LDA/6-31G(d) are given in the Supplementary information (Tables S1 and S2; additional computational details are given in Section S1). Additional data concerning C3-C, or, C3-S bond lengths has been provided in Tables S3 and S4, respectively, as it gives a qualitative description of the effect of substituent size on the *in*, as opposed to the *out* isomer. HF, as a method without included electron correlation, surprisingly, gave geometry predictions similar to MP2 and DFT. However, the relative energy difference between *in* and *out* isomers through the series of divergent levels of theory gave somewhat different results. HF and MP2 methods found greater relative stability in favour of the *in* isomer, DFT with different functionals gave a slightly smaller difference by approximately 6 kcal/mol (Table 2), and as expected MM calculations gave a substantially smaller energy difference that could not be used for definite confirmation of isomer stability (Table S1). Geometry obtained by DFTB calculations (Table S1) are comparable to DFT, albeit the energy values lie in between DFT and MM. Such results are in agreement with DFTB theory[59-61] since it represents a semi-empirical simplification of DFT and the parameters employed are calculated by DFT functionals. Similar trends respective to differences in theory were observed in geometry and energy results of [$3^{4,10}$][7]metacyclophane, Tables 3 and S2. With hydrogen as the protruding atom towards the centre of the molecule we note that all methods show greater stability of *in* isomer.

Upon introducing halogen atoms the geometrical parameters follow the previously described trend. The energy difference increases with the size of halogens and resolutely favours the *out* isomer. The C5 atom distance from the aromatic ring does not differ as much as expected between *in* and *out* isomers: for fluorine the difference is around ~0.03 Å; for chlorine ~0.5 Å and bromine ~0.7 Å.

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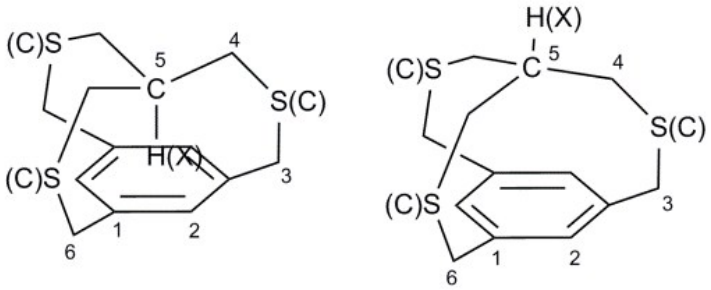

Fig. 3 *in/out*-(halogen)- 2,6,15-trithia-[$3^{4,10}$][7]metacyclophane/ $3^{4,10}$][7]meta-cyclophane with labelled atoms of interest

Table 1. Comparison of calculated bond lengths and nonbonded contacts[a,b] of in- 2,6,15-trithia-[$3^{4,10}$][7]metacyclophanes with the X ray obtained structure

Method	C1-C5	C2-C5	H(C5)-C2	C3-S	C4-S	C1-C6	C4-C5	C1-C2	MSE[c]	MUE[c]
X-ray (VAMMEB[15])	3.098	3.119	2.199	1.847	1.831	1.495	1.520	1.391		
LDA/TZP	3.065	3.096	2.184	1.838	1.822	1.485	1.516	1.389	-0.013	0.013
BP86/ 6-31G(d)	3.152	3.188	2.269	1.885	1.865	1.510	1.548	1.409	0.041	0.041
BP86-D3/ 6-31G(d)	3.124	3.158	2.245	1.879	1.858	1.508	1.542	1.408	0.028	0.028
PBE-D3/ TZP	3.136	3.170	2.254	1.874	1.854	1.505	1.540	1.402	0.029	0.029
PBE-D3/ QZ4P	3.124	3.161	2.248	1.864	1.842	1.508	1.544	1.404	0.024	0.024
M06-L/ TZP	3.119	3.151	2.247	1.858	1.841	1.495	1.531	1.392	0.017	0.017
M06-2X/ 6-31G(d)	3.119	3.148	2.245	1.844	1.825	1.497	1.530	1.395	0.013	0.015
M06-2X/ TZP	3.121	3.155	2.252	1.854	1.840	1.502	1.535	1.393	0.019	0.019
B3LYP/ 6-31G(d)	3.155	3.192	2.281	1.881	1.863	1.508	1.546	1.401	0.041	0.041
B3LYP-D3/ 6-31G(d)	3.124	3.159	2.254	1.874	1.856	1.506	1.540	1.400	0.027	0.027
B3LYP-D3/ aug-cc-pVTZ	3.112	3.147	2.244	1.869	1.848	1.500	1.535	1.394	0.019	0.019

a- bond lengths and nonbonded contacts are given in Å b- labelling of atoms is given in Figure 3 c- mean signed error (MSE), mean unsigned error (MUE) in Å

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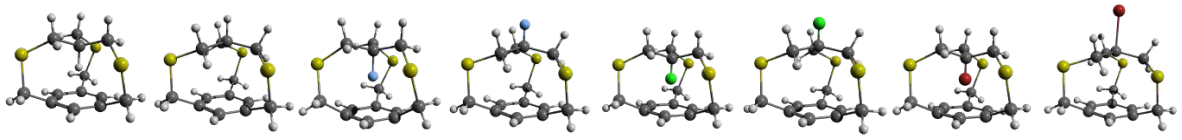

Table 2. Comparison of calculated nonbonded contacts[a,b] and relative energies[c] of in/out- 2,6,15-trithia-[3^{4,10}][7]metacyclophanes and their fluorine, chlorine and bromine containing analogues

Method		*in*-H	*out*-H	*in*-F	*out*-F	*in*-Cl	*out*-Cl	*in*-Br	*out*-Br
HF/ 3-21G	C1-C5	3.128	3.669	3.629	3.633	4.135	3.647	4.287	3.689
	C2-C5	3.158	3.701	3.679	3.664	4.182	3.680	4.316	3.722
	ΔE_{in-out}	-12.92		31.72		137.94		175.18	
HF-D3/ 3-21G	C1-C5	3.026	3.606	3.583	3.559	4.095	3.565	4.261	3.602
	C2-C5	3.051	3.636	3.631	3.588	4.144	3.595	4.291	3.633
	ΔE_{in-out}	-13.34		37.21		137.56		178.06	
MP2/ 6-31G(d)	C1-C5	3.075	3.604	3.592	3.578	4.022	3.640	4.223	3.633
	C2-C5	3.102	3.621	3.651	3.596	4.087	3.660	4.267	3.653
	ΔE_{in-out}	-11.85		34.72		125.9		168.86	
MP2-D3/ 6-31G(d)	C1-C5	2.972	3.555	3.546	3.514	3.995	3.566	4.201	3.558
	C2-C5	2.990	3.562	3.600	3.522	4.056	3.576	4.243	3.568
	ΔE_{in-out}	-13.1		40.31		123.03		168.89	
LDA/ TZP	C1-C5	3.065	3.610	3.572	3.582	4.027	3.619	-[d]	3.611
	C2-C5	3.096	3.637	3.632	3.609	4.076	3.647	-[d]	3.640
	ΔE_{in-out}	-7.48		38.37		112.01		-[d]	
BP86/ 6-31G(d)	C1-C5	3.152	3.674	3.643	3.663	4.115	3.692	4.479	3.686
	C2-C5	3.188	3.706	3.703	3.694	4.167	3.724	4.472	3.717
	ΔE_{in-out}	-7.54		33.47		115.57		142.33	
BP86-D3/ 6-31G(d)	C1-C5	3.124	3.652	3.627	3.638	4.103	3.663	4.455	3.656
	C2-C5	3.158	3.681	3.686	3.667	4.155	3.693	4.453	3.686
	ΔE_{in-out}	-7.72		35.32		116.25		143.58	
PBE-D3/ TZP	C1-C5	3.136	3.672	3.632	3.649	4.093	3.687	-[d]	3.682
	C2-C5	3.170	3.703	3.692	3.681	4.144	3.720	-[d]	3.715
	ΔE_{in-out}	-7.59		39.40		115.63		-[d]	
M06-L/ TZP	C1-C5	3.119	3.623	3.606	3.599	4.072	3.638	-[d]	3.635
	C2-C5	3.151	3.652	3.663	3.628	4.124	3.669	-[d]	3.666
	ΔE_{in-out}	-7.54		37.72		124.84		-[d]	
M06-2X/ 6-31G(d)	C1-C5	3.119	3.607	3.636	3.584	4.085	3.667	4.278	3.691
	C2-C5	3.148	3.638	3.692	3.614	4.138	3.701	4.299	3.725
	ΔE_{in-out}	-10.56		33.63		129.67		173.62	
B3LYP/ 6-31G(d)	C1-C5	3.155	3.667	3.634	3.654	4.104	3.689	4.392	3.683
	C2-C5	3.192	3.701	3.694	3.688	4.161	3.723	4.401	3.717
	ΔE_{in-out}	-8.44		33.03		125.53		161.65	
B3LYP-D3/ 6-31G(d)	C1-C5	3.124	3.641	3.617	3.626	4.092	3.657	4.408	3.650
	C2-C5	3.159	3.672	3.677	3.657	4.149	3.690	4.415	3.683
	ΔE_{in-out}	-8.81		34.95		126.19		163.08	

a- Nonbonded contacts are given in Å b- labelling of atoms is given in Figure 3 c- Relative energies between two isomers ΔE_{in-out} are given in kcal/mol d- Employed methods failed to optimize these isomers

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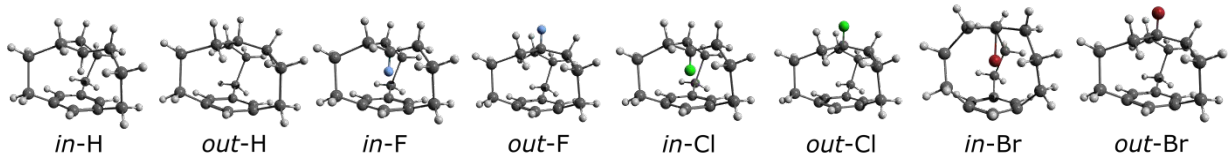

Table 3. Comparison of calculated nonbonded contacts[a,b] and relative energies[c] of *in/out*-[3[4,10]][7]metacyclophanes and their fluorine, chlorine and bromine containing analogues

Method		*in*-H	*out*-H	*in*-F	*out*-F	*in*-Cl	*out*-Cl	*in*-Br	*out*-Br
HF/ 3-21G	C1-C5	3.007	3.485	3.507	3.433	3.985	3.437	4.127	3.498
	C2-C5	3.054	3.499	3.590	3.473	4.071	3.480	4.204	3.543
	ΔE_{in-out}	-16.63		49.97		195.44		247.08	
HF-D3/ 3-21G	C1-C5	2.929	3.396	3.474	3.363	3.971	3.374	4.107	3.431
	C2-C5	2.970	3.434	3.556	3.399	4.055	3.414	4.184	3.474
	ΔE_{in-out}	-19.88		52.28		192.56		248.22	
MP2/ 6-31G(d)	C1-C5	3.008	3.445	3.512	3.436	3.923	3.492	4.095	3.483
	C2-C5	3.048	3.474	3.590	3.465	4.014	3.526	4.182	3.516
	ΔE_{in-out}	-16.06		43.84		159.74		219.22	
MP2-D3/ 6-31G(d)	C1-C5	2.922	3.380	3.476	3.363	3.914	3.419	4.079	3.410
	C2-C5	2.954	3.402	3.551	3.385	3.999	3.446	4.163	3.438
	ΔE_{in-out}	-19.07		47.12		155.58		218.48	
LDA/ TZP	C1-C5	2.998	3.442	3.484	3.431	3.905	3.462	4.086	3.451
	C2-C5	3.047	3.479	3.572	3.468	3.997	3.500	4.154	3.499
	ΔE_{in-out}	-12.38		47.22		148.71		202.20	
BP86/ 6-31G(d)	C1-C5	3.067	3.507	3.541	3.506	3.970	3.529	4.144	3.518
	C2-C5	3.119	3.548	3.632	3.546	4.067	3.572	4.222	3.561
	ΔE_{in-out}	-11.47		43.56		154.98		206.49	
BP86-D3/ 6-31G(d)	C1-C5	3.048	3.488	3.530	3.483	3.968	3.507	4.145	3.496
	C2-C5	3.099	3.527	3.621	3.523	4.065	3.549	4.225	3.538
	ΔE_{in-out}	-12.21		44.44		154.49		207.12	
PBE-D3/ TZP	C1-C5	3.059	3.508	3.534	3.497	3.957	3.523	4.144	3.513
	C2-C5	3.110	3.549	3.622	3.538	4.05	3.566	4.215	3.554
	ΔE_{in-out}	-11.68		49.25		153.30		207.58	
M06-L/ TZP	C1-C5	3.043	3.468	3.516	3.456	3.940	3.486	4.126	3.479
	C2-C5	3.091	3.503	3.603	3.492	4.037	3.524	4.204	3.517
	ΔE_{in-out}	-11.17		48.15		164.62		226.36	
M06-2X/ 6-31G(d)	C1-C5	3.035	3.464	3.526	3.462	3.947	3.527	4.100	3.533
	C2-C5	3.084	3.503	3.615	3.501	4.046	3.570	4.190	3.577
	ΔE_{in-out}	-12.42		44.18		167.34		226.54	
B3LYP/ 6-31G(d)	C1-C5	3.067	3.504	3.531	3.504	3.962	3.529	4.132	3.519
	C2-C5	3.119	3.547	3.621	3.574	4.060	3.574	4.219	3.563
	ΔE_{in-out}	-11.63		44.49		169.20		224.78	
B3LYP-D3/ 6-31G(d)	C1-C5	3.044	3.481	3.519	3.478	3.960	3.504	4.133	3.494
	C2-C5	3.095	3.522	3.609	3.518	4.057	3.547	4.220	3.537
	ΔE_{in-out}	-12.66		45.35		166.68		225.59	

a- Nonbonded contacts are given in Å b- labelling of atoms is given in Figure 3 c- Relative energies between the two isomers ΔE_{in-out} are given in kcal/mol

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3.2 EDA-NOCV

The energy decomposition analysis coupled with NOCV was performed on all the structures. The EDA results obtained using the PBE-D3/TZP functional on LDA/TZP geometries of *in/out*-halogen-[3^{4,10}][7]metacyclophane are listed in Table 4, and contours of deformational density contributions obtained via NOCV analysis are shown in Figure 4. Considering that one fragment is an atom, preparation energy originates solely from the cage fragment and can, in this case, be identified with molecular strain. Firstly, we consider the results for *in/out*-[3^{4,10}][7]metacyclophane that show a difference of ~18 kcal/mol between isomer preparation energies. This is in accordance with the claim that higher strain of the *out* isomer favours the formation of the *in* isomer.[15, 19] The combined contribution of E_{Pauli} and E_{el} is, as expected, more destabilizing in the crowded *in* isomer by ~34 kcal/mol. The orbital contribution stabilizes the *in* isomer by ~27 kcal/mol and in this instance we emphasize the influence of the orbital contribution to the formation of the *in* isomer. If the orbital energy contribution were the same as in the *out* isomer lowering of strain in the *in* isomer would not be sufficient to compensate for the great destabilizing effect of combined E_{Pauli} and E_{el}. The *in* isomers exhibit orbital stabilization that can also be visualised via NOCV deformation density contours, Figure 4, where electron density flows from the aromatic ring and cumulate in the C-H bond region.

To study whether similar interactions exist in the structures with halogens, EDA-NOCV analysis was performed (Table 4 and Figure 4) even though we proved that the *out* isomer is more stable in all cases, Table 2 and 3. As we move though the halogen series, a significant increase in the Pauli repulsion is ubiquitously observed and also the strain in the *in* isomer becomes larger than in *out* isomer due to halogen atom size. Electrostatic energy contribution is more stabilizing in the *in* isomer as substituent size increases, however insufficiently to overcome E_{Pauli}. It is important to stress that the orbital contribution is more stabilizing in the *in* isomer and NOCV analysis shows significant electron stabilization from the aromatic ring to the C-X bond. However, Pauli repulsion is the most dominant contribution in the *in* isomer. Furthermore, separate deformation density channels can be observed for investigated halogen containing cyclophanes. The distinct electronegativity of halogens is observed upon inspection of separate alpha and beta spin contributions to E^{i}_{orb}. In the case of in- fluoro-[3^{4,10}][7]metacyclophane, there is a pronounced difference between charge transfer of alpha resolution, that corresponds to the fluorine fragment, Δq=0.80 (E^{1}_{orb} =-227.41 kcal/mol), and beta resolution, that corresponds to the rest of the molecule, Δq=0.41 (E^{1}_{orb} =-227.41 kcal/mol). Similar observations can be made in case of chlorine substituated cyclophanes, although less difference between charge transfer values is observed. Moreover, bromine containing cyclophanes give almost the same values for Δq of the bromine and cage fragment. Higher charge transfer towards the halogen fragment than to the rest of the molecule, and its subtle decrease though the halogen series provides an agreeable correlation with previously known halogen chemistry.

The results of EDA-NOCV using PBE-D3/TZP, PBE-D3/Q4ZP, M06-2X/TZP, M06-L/TZP on LDA/TZP, M06-L/TZP, M06-2x/TZP and PBE-D3/QZ4P optimised geometries of in/out-2,6,15-trithia-[3^{4,10}][7]-metacyclophane, as well as EDA-NOCV analysis on the crystal structure, are shown in Tables S5, S6, S7 and S8. Most important density deformation channels using PBE-D3/TZP//LDA/TZP are given in Figure S1, while results on the X-ray structure are given in Figure S2. Based on the results, we emphasize that all employed functionals follow the same trend within the EDA-NOCV analysis, regardless even of the used geometry, or type of cyclophane. We also note that we found no significant changes of EDA-NOCV results when utilizing a larger basis set, as is seen with the PBE-D3 analysis on LDA/TZP and crystal structure with TZP (Table S5) and QZ4P (Table S8) basis set.

3.3 SAPT analysis

Geometry and proximity of the hydrogen atom to the aromatic ring in *in*-2,6,15-trithia-[3^{4,10}][7]metacyclophane and *in*-[3^{4,10}][7]metacyclophane isomers could lead to assumption of stabilizing effect of CH/π interactions in these isomers. In order to account for CH/π interactions a detailed SAPT analysis on model systems for all investigated compounds are performed and the results are presented in Table 5, S9 and S10. Data in Table 5 shows that interactions between fragments are repulsive for all *in* isomers and slightly attractive for all *out*- isomers (Tables S9, S10). This is in accordance with previous calculations on methane-benzene complex, stating that interaction becomes repulsive at methane carbon atom - aromatic ring centre (C-Ar) distances below 3.3 Å.[21-23] As expected, the largest repulsive contribution comes from exchange (Pauli) term indicating strong steric hindrance in *in*-isomers. For the model systems with hydrogen atom protruding toward the benzene ring centre dispersion and electrostatic terms are almost equal in magnitude and account for ~73 % of exchange term, thus significantly lowering the repulsive interactions. Results of SAPT analysis confirms that the main reason for higher stability of *in* isomers of 2,6,15-trithia-[3^{4,10}][7]metacyclophane and its hydrocarbon analogue is the large amount of strain present in *out* isomers, but not still enough to compensate other effects.

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Table 4. EDA-NOCV Energy Decomposition Analysis[a] using PBE-D3/TZP//LDA/TZP level of theory on in/out-[3^{4,10}][7]metacyclophane and its halogen substituted analogues

	in-H	*out*-H	*in*-F	*out*-F	*in*-Cl	*out*-Cl	*in*-Br	*out*-Br
E_{Pauli}	200.16	136.84	440.95	277.56	582.44	188.49	651.78	154.27
E_{el}	-109.25	-80.03	-181.12	-125.79	-270.53	-110.11	-312.23	-98.52
E_{orb}	-180.32	-153.31	-331.18	-270.58	-273.54	-159.95	-254.86	-123.98
$E^1_{orb}(\Delta q)^b$	-169.75 (0.95)	-144.57 (0.98)	-287.75 (1.21)	-250.36 (1.21)	-198.99(1.20)	-144.20(1.18)	-171.89(1.21)	-111.76(1.19)
$E^2_{orb}(\Delta q)^b$	-	-	-13.11(0.24)	-6.89(0.19)	-17.15(0.35)	-4.29(0.15)	-19.92(0.43)	-2.98(0.13)
$E^3_{orb}(\Delta q)^b$	-	-	-13.11(0.24)	-6.88(0.19)	-17.11(0.35)	-4.28(0.15)	-19.83(0.43)	-2.96(0.13)
E_{disp}	-1.07	-0.49	-2.18	-0.96	-3.05	-1.90	-3.01	-2.23
E_{int}	-90.48	-96.99	-73.53	-119.77	35.32	-83.47	81.68	-70.46
E_{prep}	7.07	25.17	28.43	25.04	62.75	27.93	83.05	27.38

[a] Energy components are given in kcal/mol [b] Orbital contribution is decomposed into individual contributions (E^i_{orb}) and combined for alpha and beta spin; the charge transfer through these channels, Δq, is indicated in parentheses.

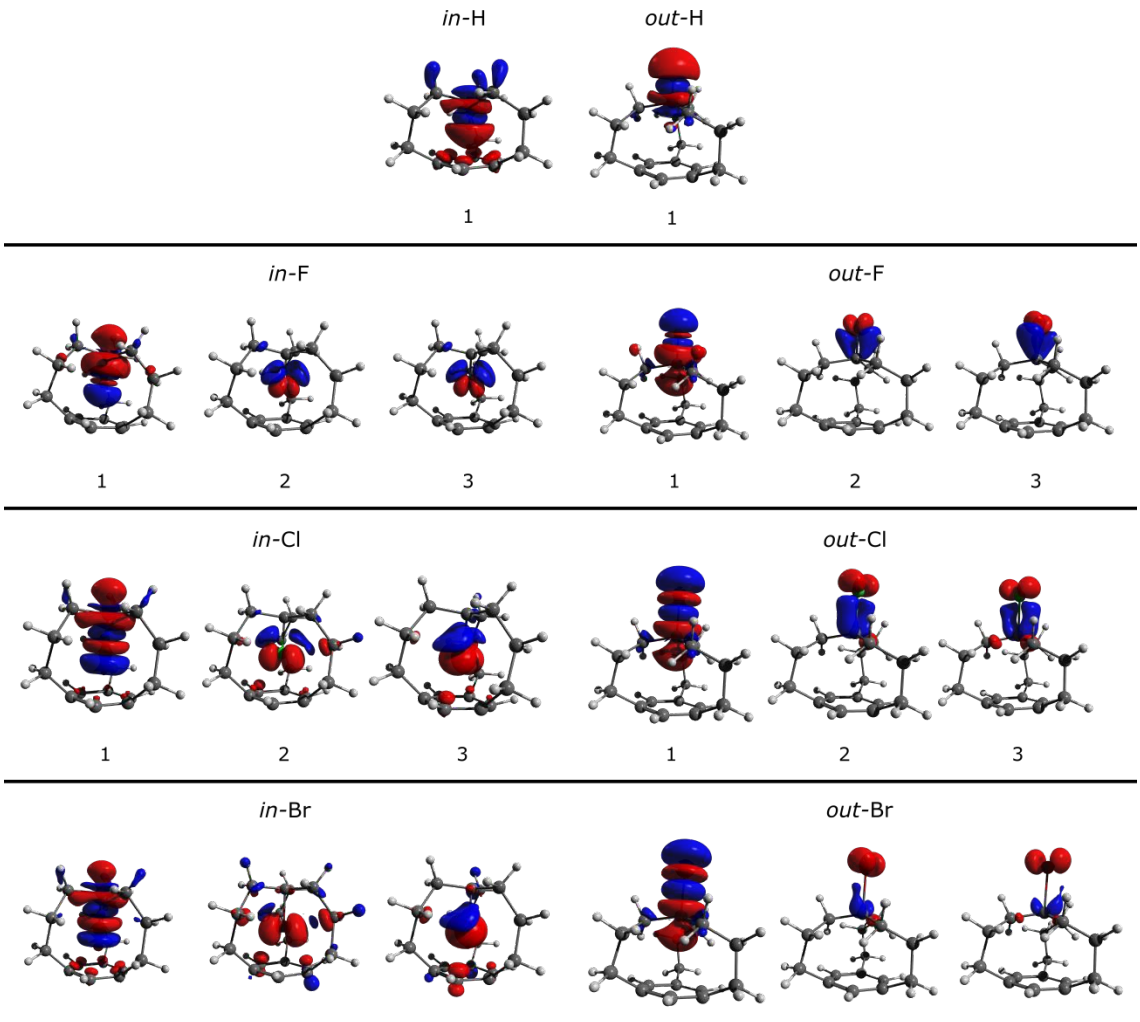

Fig. 4 Most important contours of deformation density channels obtained via NOCV analysis employing PBE-D3/TZP//LDA/TZP level of theory on [3^{4,10}][7]metacyclophane. electron flow is depicted from red to blue; isovalue 0.002au. The numbers correspond to the values of *i* in E^i_{orb}.

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Table 5. Results of SAPT analysis[b,] on model systems 1 and 2

Model system	C-Ar (Å)[a]	$E_{electrostatic}$	$E_{exchange}$	$E_{induction}$	$E_{dispersion}$	$E_{total\ SAPT}$
1	2.68	-18.17	48.81	-4.41	-17.34	8.89
2	2.75	-16.08	43.42	-3.73	-15.68	7.92

a- C-Ar distance - the distance between methane carbon atom and center of the aromatic ring; b- Energy components are given in kcal/mol

EDA-NOCV analysis was also performed on the model systems (Tables S11, S12; Fig. S3, S4) and the results are in agreement with SAPT results. Results of the SAPT analysis on model systems of halogen substituted analogues are presented in Table S9 and S10. As expected, the data shows that interaction becomes more repulsive with increasing size of halogen atom. The attractive electrostatic and dispersion energy terms can account for only 56 % (for fluorine analogue) and 62% (for chlorine and bromine analogues) of the highly repulsive exchange term. One interesting feature is the electrostatics to dispersion ratio: for fluorine analogue electrostatic energy term is only 1.4 times larger than dispersion; for chlorine 2.1 and for bromine 2.4. This is in accordance with existence of positive σ-hole on chlorine and bromine atom, but not on fluorine atom.[62]

4 Conclusions

In this paper we summarize the efforts to theoretically explain the unusual chemistry of cyclophanes, which have been described as strained and crowded molecules. In order to provide a detailed account on computational chemistry methods employed, a divergent set of methods was chosen, ranging from molecular mechanics through semi-empirical to *ab intio*. We found that DFT is generally reliable for the description of cyclophane chemistry, not only for geometries but also for the relative isomer stabilities and EDA analysis. We also noted an unusual proximity of the methine carbon to the aromatic ring in the *in* isomer that was further investigated by harnessing capabilities of the EDA-NOCV and SAPT analysis. Even though these methods are theoretically quite different (one is variational while the other is perturbational) the same conclusion has been drawn: the greater stability of the *in* isomer of 2,6,15-trithia-[$3^{4,10}$][7]metacyclophane and [$3^{4,10}$][7]metacyclophane originates not solely from the strain reduction, but also from orbital stabilization through the density different channel with the participation of the aromatic ring electron density. On the other hand when the methine hydrogen was substituted with halogens (fluorine, chlorine and bromine) we found that the *out* isomer is more stable in all structures. In these cases, the destabilizing effects due to the Pauli (exchange) term and strain were far too large to be overcome by other stabilizing contributions. The stabilizing orbital energy contribution favoured the *in* isomer and NOCV density deformation contours showed a favourable interaction between aromatic density and the C-X bond.

The work presented herein confirms that all the employed methods gave satisfactory results, and a full understanding of such subtle interactions is given through EDA-NOCV and SAPT analysis. This is of utmost importance, since fine tuning of electronic and steric contributions could lead to creation of novel cage compounds with desired properties suitable for application in versatile fields.

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